The Norfolk Arthritis Register (NOAR)

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ABSTRACT

The Norfolk Arthritis Register (NOAR) has been recruiting and following patients with early inflammatory polyarthritis (IP) since 1989. Approximately three-quarters of the patients followed satisfy classification criteria for rheumatoid arthritis (RA) by 5 years from symptom onset. This paper summarises the publications which have been based on the NOAR cohort with respect to the incidence and prevalence of IP and RA, genetic and environmental risk factors for the development of IP, outcome following the development of IP and predictors of outcome. It also discusses methodological issues in examining the treatment effect in observational cohorts and the costs to the healthcare system of patients with early IP.

Introduction

The Norfolk Arthritis Register (NOAR) was established during 1989. By the beginning of 1990, all the general practitioners (GPs) in what was then the Norwich Health Authority had been visited and asked to participate. A team of metrologists (research nurses and a research occupational therapist) had been recruited and trained to take a standardised history and examine joints for tenderness, swelling and deformity in a reproducible way. From 1 January 1990, the GPs and local rheumatologists referred to NOAR all adults (age ≥16) who they saw with two or more swollen joints, lasting for 4 or more weeks, with an onset since 1 January 1989. This date (1/1/89) has never been changed.

The patients are visited at home by a metrologist who completes the baseline questionnaire, examines the joints and takes blood for rheumatoid factor (RF) measurement and DNA extraction. These blood tests are performed at the University of Manchester. The patient completes a Health Assessment Questionnaire (HAQ) (1) adapted for British use (2).

The patients have been followed annually for 5 years by the metrologists. The American College of Rheumatology (ACR) 1987 classification criteria for rheumatoid arthritis (RA) (3) are applied cross-sectionally at each visit and cumulatively at 5 years. The patients are seen and examined at the 1st, 2nd, 3rd and 5th anniversary. The 4th anniversary assessment is performed by telephone. X-rays of the hands and feet are performed on those patients who have already satisfied the ACR criteria or in whom the finding of radiological erosions would enable them to satisfy the ACR criteria at the 1st anniversary visit – and at the 2nd anniversary visit if the 1st anniversary X-rays are non-erosive. All patients complete a HAQ at each year of follow-up. The 5th anniversary visit is more comprehensive and includes completion of the SF-36 (4) and a visual analogue pain score. Patients are next seen and assessed at the 7th anniversary and then at the 10th anniversary.

All patients recruited between 1990 and 1994 (Phase Ia) remain under long-term follow-up. The exceptions are those patients who did not cumulatively satisfy the ACR criteria for RA at 5 years and who had been given a consultant diagnosis other than RA, undifferentiated inflammatory polyarthritis (IP), psoriatic arthritis or post-viral arthritis to explain their symptoms. Patients whose disease had gone into spontaneous long-term remission (no inflamed joints at the 3rd or 5th anniversary and not on disease modifying anti-rheumatic drugs (DMARDs) or steroids) are not followed beyond the fifth anniversary.

Between 1995 and 1999 (Phase Ib), patients recruited by NOAR were followed only for two years from symptom onset. The exceptions were patients referred to NOAR within 3 months of symptom onset; patients with a history of psoriasis; men aged 45

or under; and women aged 35 or under. These four groups (who comprised about one-third of all referrals) are being followed long-term as described for Phase Ia.

Since 2000, all patients referred to NOAR are again being followed long-term (Phase Ic). However, since the beginning of 2002, the number of recruiting GPs has been reduced by two-thirds. All new patients with IP seen at the Norfolk and Norwich University Hospitals are still being recruited.

Purpose of this paper

This paper summarises the key results which have emerged from NOAR since its inception in 1990. Many of the observations made on the NOAR cohort have confirmed associations or predictors reported elsewhere. This paper is not intended to provide an overview of the epidemiology of inflammatory polyarthritis or RA and so we have not included references to other studies which may have demonstrated similar – or sometimes contradictory – results.

Classification of RA

NOAR was established fairly soon after the publication of the 1987 ACR criteria for RA (3). Initially, we assumed that these criteria would identify which patients in the NOAR cohort did and did not have RA – hence the rules for X-raying patients at the 1st and 2nd anniversary (described above). However, it soon became apparent that the ACR criteria do not perform well in this setting (5). This is not surprising given that the criteria were developed by distinguishing patients with established RA from other patients with other musculoskeletal disorders, which means that they are best suited to classify people with established RA.

We found that the ACR criteria, applied at the baseline NOAR visit, had little more than random ability to predict the persistence of arthritis, the development of radiologic erosions or of moderate disability (HAQ score ≥1) (5). Patients continue to satisfy the ACR criteria for RA when applied cumulatively for up to 5 years (6). The proportion of NOAR cases who satisfy the ACR criteria for RA cumulatively by 5 years is around twice the proportion who satisfy them at baseline (6). We have recently suggested that the term "early RA" is inappropriate and should not be used in this context (7).

The occurrence of RA

The first incidence data from NOAR were published in 1994 (8). They were based on the patients who presented to NOAR in 1990 and 1991 and applied the ACR criteria cross-sectionally at baseline. The annual incidence of RA based on the state at baseline was 36 per 100,000 in women and 14 per 100,000 in men. The five-year follow-up data have been used to refine these estimates. Applying the ACR criteria cumulatively over 5 years gives annual incidence estimates of 54.0 per 100,000 for women and 24.5 per 100,000 for men (6).

In 2000 we conducted a two-stage cross-sectional survey to establish the prevalence of RA in Norfolk. The sample of 7,050 adults was selected from GP practices who notify to NOAR. Weighted back to the general population the study found an overall prevalence of RA, using the 1987 ACR criteria, of 0.81% in adults. The prevalence was 11.6 per 1000 in women and 4.4 per 1000 in men (9). The prevalence in women had fallen since the previous UK estimates performed by John Lawrence in the 1950's, but had remained stable in men (10).

Environmental risk factors and the development of IP

Influence of person, time and place

The fact that NOAR cases are being notified continuously from a defined population has enabled us to look for evidence of the clustering of cases in time and space. There was no evidence that, in general, new cases of IP occur in clusters (11). However, although clustering does not explain the majority of IP cases, three small clusters of cases in place have been observed and described (12). The cases within each cluster were not phenotypically similar and did not present close together in time. It is difficult to say whether or not they are true clusters or may have occurred by chance.

NOAR data suggest that the distribution of age at onset of IP and RA is older than was described 50 years ago (6,8). The peak age of onset is 65-75 in women and over 75 in men. In fact, the age-specific incidence of RA in older men (aged 75 and over) was higher than in women of the same age. We found no evidence of an influence of socio-economic status on the incidence of RA (13).

Influence of infection and immunisation

A sero-epidemiological study of NOAR IP cases notified soon after symptom onset found only a very small number with evidence of recent parvovirus infection (14). There was, however, evidence of a higher than expected frequency of tetanus immunisation in the 6 weeks prior to IP onset (15, 16).

Influence of lifestyle factors

In 1994-1995, we conducted a case-control study to investigate a variety of putative risk factors for IP (16). The cases were 165 patients aged 18-70 referred to NOAR between May 1994 and April 1995 within 12 months of symptom onset. The 178 controls were taken from the combined registers of all GPs referring to NOAR and were matched to the cases by gender and date of birth. Two controls per case were recruited for men aged under 45. This study found that smoking (ever) (adjusted OR = 1.7, 95% CI 1.0-3.1) and obesity (BMI > 30) (adjusted OR = 3.7, 95% CI 1.1 – 12.3) were risk factors for the development of IP.

More recently, we have benefited from the fact that another epidemiological study is being conducted using the same denominator population. The European Prospective Investigation of Cancer (EPIC-Norfolk) study has recruited 25,000 adults aged over 45. Participants in the EPIC-Norfolk study are interviewed with regard to a number of exposures and complete an intensive dietary assessment including a seven-day record of food intake. By running the NOAR and EPIC-Norfolk databases against one another, we were able to identify 73 EPIC-Norfolk participants who had developed IP and

been referred to NOAR after their EPIC assessment. Each was matched to an EPIC control without IP (matched for age, gender and time of recruitment to EPIC). This study confirmed the previously observed link between smoking and IP (16). It also found that EPIC participants in the lowest tertile of vitamin C intake had an odds of 4.1 (95% CI 1.7–9.7) of developing IP compared to those in the highest tertile of intake (17). We also examined traditional cardiovascular risk factors in these NOAR patients prior to the onset of IP and, apart from smoking, found no difference between the cases and controls (18).

The use of the EPIC-NOAR link also enabled us to look at the connection between early life events and the subsequent development of IP (19). No links were found but, because of the EPIC study design, IP cases were confined to those with an onset after age 45.

Influence of hormonal factors

The results of the NOAR case-control study confirmed the observation of a number of other studies, showing a protective effect against the development of IP in current users of the oral contraceptive pill (OR 0.2, 95% CI 0.1-0.9) (20). There was no evidence of a link with nulliparity (OR 0.8, 95% CI 0.3-1.2) but the NOAR cases did report a higher rate of miscarriage (OR 2.2; 95% CI 0.9-5.5) (21) and termination of pregnancy (OR 3.7; 95% CI 1.6-8.6) (19) than age matched controls from the local population. There was no evidence of a link between menopausal status or the use of hormone replacement therapy and the development of IP.

Influence of medical factors

The NOAR case-control study reported the intriguing finding of an association between prior blood transfusion and the development of IP (especially RF positive IP) (adjusted OR = 4.8, 95% CI 1.3-18.1) (16). In addition, a modest association between psoriasis and IP was noted. However, although we have found that psoriasis and immunisation are potential triggers of IP, there was no evidence that the pattern of arthritis at presentation or the short-term outcome was any different in patients whose IP may have been triggered by psoriasis (22) or immunisation (23) than in those without those triggers.

Genetic risk factors for the development of IP

The design of NOAR makes it possible to distinguish between those genetic factors which influence susceptibility to IP and those which influence persistence or disease severity. In 1993, we conducted a family study in patients newly referred to NOAR, using their friends as the controls. We found that the occurrence of RA was not increased in the first degree relatives of the NOAR cases (24). A preliminary analysis of the first year of notifications to NOAR (n=208) showed only weak associations between HLA-DR B1*04 and DRB*01 (25). This first study did not include subtyping of HLA-DRB1*04.

A later larger study included 608 consecutive NOAR patients with IP (404 satisfied the ACR criteria for RA) (26). The frequencies of various shared epitope (SE) alleles were compared with those in 298 local adult controls. As before, only a modest association was found between IP and any copy of the SE (OR 1.8; 95% CI 1.4-2.4). The effect of being homozygous for the SE was only moderately greater than the effect of being heterozygous. However, the risk of being RF positive was substantially higher in those who were homozygous for the SE. All the individual alleles containing the SE showed a similar level of association with IP except for *0404 (OR 3.5; 95% CI 1.8-6.8). Individuals who were homozygous for *0404 had an OR of 17.9 (95% CI 4.2-77.8) of developing IP. Thus, it does appear that *0404 is a susceptibility factor for IP. The association between *0404 and RA was no stronger than the association with IP.

Outcome following the onset of IP

The NOAR dataset has been used to address questions about the occurrence of a variety of outcomes at 1, 3 and 5 years, and predictors of those outcomes (27).

Remission

There are problems regarding the definition of remission and resolution of IP. The short-term remission (at one and two years after notification) was surprisingly low and it was difficult to predict which patients would go into remission with any degree of accuracy (28).

Disability

We have looked at the occurrence and predictors of disability at one (29), three (28) and five years (30-32). We found that disability cannot be tracked from year to year – that is, those patients, for example, in the 75th centile at year one will not necessarily be in the 75th centile at year 5 (30). The key risk factors for the development of disability (HAQ $\geq$ 1.0) at 5 years are being female, age over 64, the number of damaged joints, RF positivity and the presence of nodules (32). However, one of the strongest predictors of disability at 5 years was disability earlier in the course of the disease. The HAQ score at one year was substantially more predictive than the HAQ score at baseline (31), suggesting that there are opportunities in the first year of disease to influence permanently the long term outcome.

We published data on the 5-year outcome using the HAQ, SF-36 and pain score as a benchmarking exercise (33). The aim was to provide population-based data to be used as a reference when assessing the impact of newer therapeutic agents for RA.

Work disability

We have examined the impact of IP and RA on the ability to remain in employment (34). Two cohorts of patients were studied: 160 with an onset between 1989-1992 and 134 with an onset between 1994-1997. In the first cohort, 14% and 26% were work disabled by one and two years respectively; and in the more recent cohort 23% and 33%. The HAQ score at baseline was one of the strongest predictors of work disability.

Radiological outcome

Again radiological outcome has been studied at one (35), three (27) and five

years (36-38). The older literature suggested that those patients with RA who are going to develop erosions always develop their first erosions within two years of disease onset. This hypothesis had never been tested in a cohort in which a substantial proportion were non-erosive at 2 years, nor has it been re-examined since the shift in approach to the use of more powerful DMARDs earlier in the disease course. We were able to show that, although the peak incidence of first erosions is in the first 24 months, individuals who are non-erosive at 24 months have an ongoing risk of becoming erosive which does not decline with time (36). Baseline CRP was a key predictor of the severity of erosive damage at both the first year and fifth year anniversary films. An RF titre greater than 1/160 was the strongest predictor of X-ray progression (38).

Mortality

We had anticipated that mortality in this primary-care based inception cohort of IP patients treated in the modern era of early initiation of DMARDS would not be increased. However, this was not the case. Among the first 1,235 subjects recruited in the NOAR study, there were 159 deaths during a median follow-up period of 6.9 years (39). The standardised mortality ratios (SMR) in the seropositive patients were 1.5 for men and 1.4 for women. Virtually all the excess deaths in seropositive women were due to cardiovascular causes. The SMR for cardiovascular mortality in women was 2.0 (95% CI 1.2-3.3). Smoking was not a predictor of cardiovascular mortality in the seropositive patients.

Genetic and environmental predictors of outcome

Genetic

The influence of the SE on disease outcome at 2 years in IP has been explored in the NOAR cohort (40). There was no evidence that the SE (or any particular SE-bearing allele) had any influence on disease persistence. The presence of SE alleles had a modest influence on the development of functional disability (HAQ score ≥1.0). The effect was restricted to those who were RF negative. The most obvious link was between the SE and the development of radiological erosions (RR 1.9; 95% CI 1.4-2.6 for one copy of the SE; RR 2.5; 95% CI 1.8-3.6 for two copies of the SE). Again, this effect was restricted to those who were RF negative. The strongest association was with *0404/*0404 homozygosity (RR 4.2; 95% CI 2.0-8.5).

A very similar pattern was seen when we explored the link between SE alleles and mortality (41). IP patients with two copies of the SE had increased mortality from all causes and from cardiovascular causes over the first 8 years of disease compared to those who were SE negative. On stratification, it was found that the effect was seen only in those who were RF negative. Seronegative patients with 2 copies of HLA DRB *04 had increased cardiovascular mortality (hazard radio 3.2; 95% CI 1.2-8.1).

We have now started to explore the influence of non-HLA genes on disease outcome (42). No link was found between any TNFα alleles or carriage of the 32 bp CCR5 deletion and the development or severity of erosions at 5 years.

Environmental

We have examined the effect of cigarette smoking on disease outcome (43). Although smokers had a worse HAQ score, they actually had lower tender and swollen joint counts and less radiologic progression than non-smokers. This raises the possibility that smoking has anti-inflammatory properties.

Treatment

It is very difficult to explore the effects of treatment in longitudinal observational cohorts. This is because the decision to treat is not random, treatment being targeted at those with the most severe disease. Unless treatment is so effective as to negate all the effects of disease severity that led to the decision to start treatment, then those who are treated are likely to have a worse outcome than those whose disease was so mild as not to warrant therapy. The propensity score offers a way of adjusting for the baseline severity which influences the decision to start treatment. We have used this method to demonstrate the benefit of early treatment (within 6 months of symptom onset) on functional (44) and radiological (45) outcome. We also used this methodology to explore the influence of the shared epitope (SE) on treatment response (46). It appears that (after allowing for the fact that they have milder disease at baseline) patients who are SE negative are less likely to respond to treatment than those who are SE positive.

The costs of RA and IP

Finally, we have explored the costs of early IP to the individual and society. A questionnaire has been developed which is specific for health economics studies in RA and IP patients (47). This was used to gather information on the total costs during the first five years of IP (48). A separate study identified the secondary care and DMARD monitoring costs (49). In brief, it was found that a small proportion of patients generated the great majority of costs. The HAQ score at baseline was an important predictor of costs.

Conclusion

Information generated by the NOAR study has contributed to our understanding of the occurrence and outcome of IP. It has also provided insights into genetic and environmental predictors of the onset and outcome of the disease. Future work will focus on the outcome beyond 5 years,further exploration of the response to and benefits of treatment, and the links between IP and other co-morbidities such as cardiovascular disease.

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